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Oncoproteins double-team and destroy vital tumor-suppressor

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Two previously unconnected cancer-promoting proteins team up to ambush a critical tumor suppressor by evicting it from the cell's nucleus and then marking it for death by a protein-shredding mechanism, a team led by scientists at The University of Texas M. D. Anderson Cancer Center reports in the Feb. 10 issue of *Nature Cell Biology*.

The paper is the first to illuminate a mechanism of attack on FOXO3a, a member of the forkhead family of tumor-suppressing proteins, notes senior author Mien-Chie Hung, Ph.D., chair of M. D. Anderson's Department of Molecular and Cellular Oncology.

"We know that FOXO3a is inactivated in about 80 percent of breast tumors, and that it's likely to be inactivated in other solid tumors because three major oncogenic pathways separately target it," Hung said. "The implication is that forkhead activation will be a great therapeutic target because it would be a powerful tumor-suppressor."

Hung and colleagues focused on the effect of the RAS-ERK signaling pathway, which is known to promote tumor growth and proliferation. FOXO3a and its other forkhead cousins have a specific structure - the forkhead box - that allows them to connect with DNA. They are transcription factors, activating or repressing target genes involved in tumor suppression and DNA damage repair.

The team shows in a series of lab experiments that ERK attaches phosphate groups to three specific sites on FOXO3a. This

phosphorylated version of FOXO3a is hijacked out of the nucleus, so it can no longer do its job transcribing tumor-suppressing-genes.

Enter the second oncogenic protein, MDM2. MDM2, the team shows, only recognizes the phosphorylated version of FOXO3a. By attaching a string of targeting proteins known as ubiquitins to the phosphorylated tumor suppressor, MDM2 marks it for destruction by the ubiquitin-proteasome degradation pathway.

"Both ERK and MDM2 are well-known oncoproteins, but their collaboration was previously unknown," Hung said.

In a sample of 125 breast cancer tumors, the researchers found that high MDM2 expression and low FOXO3a expression are associated with higher grade tumors.

Additional experiments showed that breast cancer cells treated with healthy FOXO3a and injected into mice resulted in barely measurable tumor volumes after 56 days. Mice injected with cells featuring a disabled version of the tumor-suppressor had an average volume of more than 600 cubic millimeters.

ERK, AKT and IKKß are three separate cancer-causing kinases - proteins that phosphorylate other proteins - that Hung calls the Three Musketeers of cancer. All three target FOXO3a. "At least one of these pathways is active in at least 80 percent of solid tumor cancers," Hung says. "ERK alone accounts for 30 percent of human cancers."

"Pharmaceutical companies work to target ERK, AKT and IKKß separately," Hung notes. "But activating their forkhead target would work against all three of them. Enhancing FOXO3a could be an effective therapeutic strategy."

Source: University of Texas M. D. Anderson Cancer Center